[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

THE CHLORO-α,α-DIPHENYLACETONES. PREPARATION, PROOF OF STRUCTURE, AND REACTIONS WITH BASE[1]

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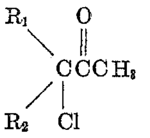
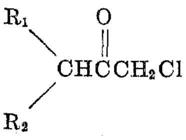
Received April 23, 1952

The results reported in this paper are a continuation of the investigation of the chemistry of α-halocarbonyl compounds. The object of the present work was the preparation, proof of structure, and reaction with base of the isomeric chloro-α,α-diphenylacetones (I and II).

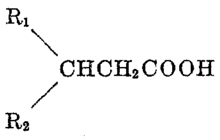
Some years ago Richard (1) reported that the chloroketones I, IV, and VII could be transformed by treatment with base into the acids III, VI, and IX respectively.



I $R_1 = R_2 = C_6H_5$
IV $R_1 = C_6H_5$; $R_2 = H$
VII $R_1 = C_6H_5CH_2$; $R_2 = H$



II $R_1 = R_2 = C_6H_5$
V $R_1 = C_6H_5$; $R_2 = H$
VIII $R_1 = C_6H_5CH_2$; $R_2 = H$



III $R_1 = R_2 = C_6H_5$
VI $R_1 = C_6H_5$; $R_2 = H$
IX $R_1 = C_6H_5CH_2$; $R_2 = H$

Later McPhee and Klingsberg (2) confirmed the conversion of IV to VI and extended the investigation to include the transformation of V to VI. However, these authors were unable to confirm the reaction of VII to IX as reported by Richard and further they were unable to synthesize I in useful yields for further investigation.

Richard reported the preparation of α-chloro-α,α-diphenylacetone (I) by the chlorination of α,α-diphenylacetone with sulfuryl chloride but reported neither yield nor proof of structure. Since bromination of diphenylacetone has been shown to give either of the two isomeric monobromoketones in good yield by variation of the temperature of reaction (3), an unequivocal synthesis of I and II was indicated. These chloroketones (I and II) were synthesized, the structures proven, and the reaction of each with base shown to give the acid (III).

α-Chloro-α,α-diphenylacetone was synthesized by the series of reactions X $\rightarrow$ XIII $\rightarrow$ I.

Ethyl pyruvate (X) was converted to the ketal (XI) in 79% yield using ethyl orthoformate and an acid catalyst. The ketal ester (XI) when allowed to react with phenylmagnesium bromide was converted smoothly to the tertiary alcohol (XII). This crystalline alcohol was isolated in 62% yield and was characterized by carbon, hydrogen, and methoxyl analysis as well as the preparation of ketone derivatives in acid solution. An infrared spectrum (Fig. 1) showed

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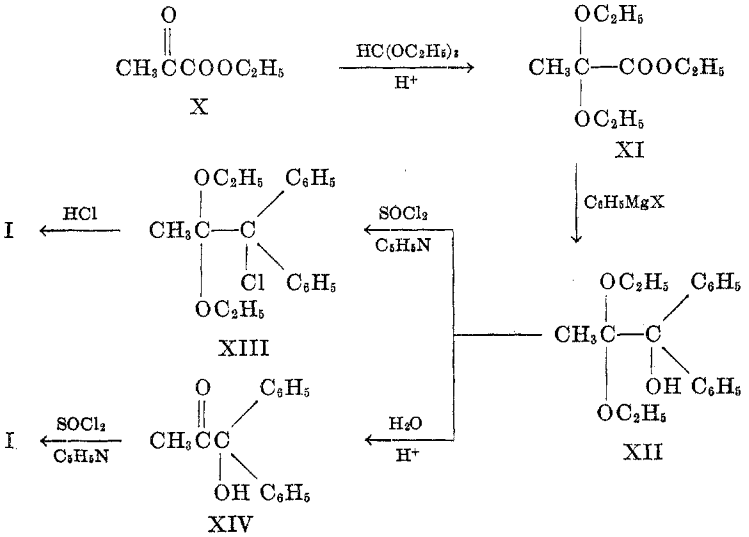
[1] This work was supported in part by the Research Corporation of New York.



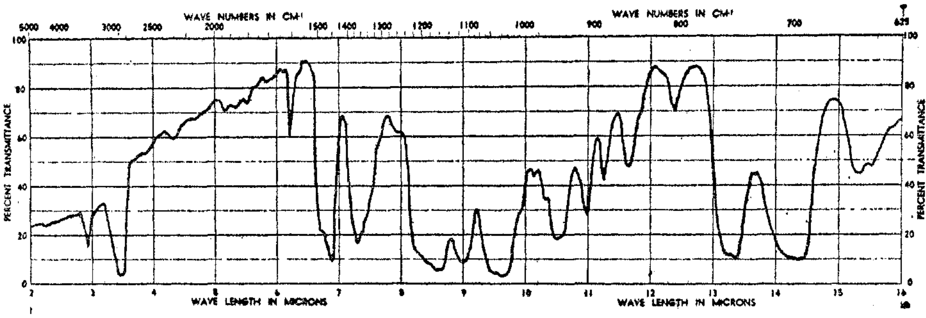


FIG. 1. INFRARED ABSORPTION SPECTRUM OF 1,1-DIPHENYL-2,2-DIETHOXYPROPANOL-1 (XII) TAKEN AS A MULL IN MINERAL OIL[2]

clearly a hydroxyl band but no band corresponding to a carbonyl group. It is interesting to note that Seifert, *et al.* (4) isolated only the ketal ketone from the reaction of the diethyl ketal of ethyl α-ketobutyrate and two moles of methylmagnesium iodide.

The hydroxy ketal (XII) was converted to a chloro ketal (XIII) by treatment with thionyl chloride and pyridine. The ketal group remained intact since the product contained the correct ethoxyl content for XIII. The yield of crystalline chloro ketal (XIII) was 77%. When treated with dry hydrogen chloride the ketal group of XIII was cleaved and α-chloro-α,α-diphenylacetone (I) could be isolated in 67% yield.

This sequence of reactions is considered to prove the structure of I and the yields are sufficient to provide material in useful amounts.

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[2] Courtesy of Dr. L. E. Kuentzel and Miss D. Orlowski, Wyandotte Chemicals Corp., Wyandotte, Michigan.

An alternate path from XII to I involved hydrolysis of the hydroxy ketal (XII) with dilute acid to give 98% of crystalline α-hydroxyketone (XIV) followed by reaction of XIV with thionyl chloride in pyridine from which 83% of I was isolated.

The α-hydroxy-α,α-diphenylacetone (XIV) was identical with the hydroxyketone isolated by Temnikova (5) from the bromination of α,α-diphenylacetone followed by hydrolysis. The present series of reactions is considered to prove the structure of XII.

When α-chloro-α,α-diphenylacetone (I) was allowed to react with finely divided sodium hydroxide in ether, β,β-diphenylpropionic acid (III) was isolated in 55% yield along with 25% of unreacted I. Sodium ethoxide in absolute alcohol reacted more rapidly with the chloro ketone (I) to give ethyl β,β-diphenylpropionate in 85% yield. The ester was identified by boiling point, melting point, ethoxyl analysis, and hydrolysis to the acid (III).

α′-Chloro-α,α-diphenylacetone (II) was prepared from diphenylacetyl chloride by first preparing the diazoketone using two equivalents of diazomethane and following the procedure of McPhee and Klingsberg (6). Dry hydrogen chloride gas converted the diazoketone to the chloro ketone in 85% yield from the acid chloride. Lewis, Nierenstein, and Rich (7) report a significantly higher melting point for this chloro ketone from a reaction using only one equivalent of diazomethane. In common with other workers (2, 8) these results could not be repeated in this laboratory.

Although the isomeric chloro ketones I and II had virtually the same melting point, the melting point of a mixture was greatly depressed.

When the chloro ketone II was allowed to react with sodium ethoxide in absolute alcohol under the same conditions as chloro ketone I, the ethyl ester of β,β-diphenylpropionic acid was isolated in 69% yield. However, from this reaction a 12% yield of diphenylacetic acid could be isolated, along with a small amount of another acid which was not identified.

The formation of the ester of β,β-diphenylpropionic acid from both chloro ketones (I and II) can be satisfactorily explained by the cyclopropanone intermediate mechanism (9, 10).

EXPERIMENTAL

Ethyl pyruvate (X). Freshly distilled pyruvic acid (96 g., 1.1 moles, $n_D^{15.5}$ 1.4315) was esterified with 79 g. (1.7 moles) of absolute ethyl alcohol without the aid of the usual inorganic acid catalyst by adding 185 ml. of benzene to the reaction mixture and using a water separator to eliminate water. Distillation of the reaction mixture gave 110 g. (95%) of ethyl pyruvate, b.p. 63–69° (32 mm.); $n_D^{15.6}$ 1.4096. Watson and Yates (11) report b.p. 63–65° (23 mm.); $n_D^{15.6}$ 1.4083.

Ethyl α,α-diethoxypropionate (XI). In a 300-ml. flask fitted with a reflux condenser and a calcium chloride tube were placed 52 g. (0.45 mole) of ethyl pyruvate, 111 g. (0.75 mole) of ethyl orthoformate, 92 g. (2 moles) of absolute ethyl alcohol, and 5 drops of concentrated sulfuric acid. The mixture was allowed to stand for 24 hours, and then refluxed for eight hours. The liquid was separated from the acid catalyst by distillation with a minimum amount of heat from the reaction flask into another flask immersed in a Dry-Ice bath, first using a water aspirator at 30 mm. and then a vacuum pump at 1 mm. The liquid was then fractionated to give 152 g. (79%) of ethyl α,α-diethoxypropionate, b.p. 93–94° (26 mm.); n_D^{25} 1.4115; d_4^{22} 0.9750. Claisen (12) reports the compound to have b.p. 190–191° (dec.); $d_4^{18.2}$ 0.9783; n_D^{25} 1.4118.

1,1-Diphenyl-2,2-diethoxypropanol-1 (XII). In a 2-l., three-necked, Morton Flask (13) fitted with a reflux condenser, calcium chloride tube, a stirrer, and a 100-ml. dropping-funnel, were placed 38 g. (1.58 moles) of magnesium turnings and sufficient anhydrous ether to completely cover the magnesium. Through the dropping-funnel 273 g. (1.74 moles) of bromobenzene in 275 ml. anhydrous ether was added. The addition took about two hours, and upon its completion the flask was heated an additional three hours. The flask was cooled and 150 g. (0.79 mole) of ethyl α,α-diethoxypropionate in 250 ml. of anhydrous ether was slowly added with constant stirring. This addition took about two hours, and after completion the mixture was refluxed two hours. During the addition the contents of the flask slowly turned white. The mixture was then hydrolyzed by the addition of four 200-ml. portions of saturated ammonium chloride solution, after which the aqueous layer was extracted several times with ether. The ether extracts were combined and dried over sodium sulfate, and then the ether was distilled. Distillation of the remainder of the liquid gave a forerun of 58 g., b.p. 50–135° (1 mm.) followed by 151 g. of 1,1-diphenyl-2,2-diethoxypropanol-1 (XII), b.p. 131–160° (1 mm.). The latter fraction solidified and was recrystallized from ethyl alcohol to give 143 g. (61.5%) of white crystals, m.p. 72–74°. Redistillation of a small portion gave analytically pure hydroxy ketal, b.p. 135–137° (0.6 mm.), m.p. 73–74°. The supercooled liquid had n_D^{25} 1.5490, d_4^{30} 1.0522.

Anal. Calc'd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00; OC_2H_5, 30.00.
Found: C, 76.12; H, 7.89; OC_2H_5, 29.78.

Preparation of α-hydroxy-α,α-diphenylacetone (XIV). In a 50-ml. round-bottomed flask fitted with a reflux condenser was placed 0.5 g. of 1,1-diphenyl-2,2-diethoxypropanol-1. To the hydroxy ketal was added 10 ml. of 95% ethanol and 10 ml. of 1:1 hydrochloric acid. The mixture was refluxed three hours, and the solvent distilled at room temperature under 3 mm. pressure. A light brown precipitate remained, which when dried had m.p. 60–62°. After recrystallization from ether, and then from acetone cooled in Dry Ice, 0.37 g. (98%) of white crystals were obtained, m.p. 66–67°. Temnikova (5) reports this compound to have m.p. 65–66°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.65; H, 6.19.
Found: C, 79.69; H, 6.22.

The *oxime* was prepared in 80% yield, m.p. 161–162°.

The *semicarbazone*, m.p. 174–176° was prepared in 80% yield.

The mixture melting points of these derivatives and the derivatives made from the hydroxy ketal (XII) were not depressed.

Temnikova (5) reports the *oxime*, m.p. 159–160° and the *semicarbazone*, m.p. 176–177°.

1-Chloro-1,1-diphenyl-2,2-diethoxypropane (XIII). In the usual apparatus were placed 25 ml. of benzene, 7 g. (0.023 mole) of 1,1-diphenyl-2,2-diethoxypropanol-1, and 1.85 g. (0.023 mole) of anhydrous pyridine. The flask was placed in an ice-bath and cooled to 0°, and in the dropping-funnel was placed 2.78 g. (0.023 mole) thionyl chloride in 5 ml. of benzene. During the addition of the thionyl chloride a white solid was formed which went into solution as more thionyl chloride was added. After the addition, the flask was heated at 50–60° for three hours. Ice was added with stirring, the layers were separated, and the benzene layer washed twice with sodium bicarbonate, 1% hydrochloric acid, and water. After the benzene layer was dried over magnesium sulfate, the solvent was removed at room temperature with a water aspirator. A brown solid remained which was purified by recrystallization from heptane followed by acetone cooled in Dry Ice to give 5.35 g. (76.5%) of the white crystalline 1-chloro-1,1-diphenyl-2,2-diethoxypropane (XIII), m.p. 71–72°.

Anal. Calc'd for $C_{19}H_{23}ClO_2$: Cl, 11.14; OC_2H_5, 28.27.
Found: Cl, 11.39; OC_2H_5, 28.38.

Preparation of α-chloro-α,α-diphenylacetone (I). *a. From the chloro ketal* (XIII). Anhydrous hydrogen chloride was passed through a 125-ml. Erlenmeyer flask one-half filled with concentrated sulfuric acid and then into a six-inch test tube in which was placed 0.4 g. of 1-chloro-1,1-diphenyl-2,2-diethoxypropane (XIII). The hydrogen chloride was allowed to leave the test tube through a three-foot length of glass tubing, the outer end of which contained anhydrous calcium chloride. The chloro ketal was liquified by immersion of the test tube in hot water, and the hydrogen chloride was passed into the liquefied ketal for three hours. At the end of this time, crystals appeared in the test tube on cooling. This solid was recrystallized from heptane and then from acetone cooled in Dry Ice to give 0.2 g. (67%) of the desired α-chloro-α,α-diphenylacetone (I) m.p. 65–66°.

Anal. Calc'd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.31; Cl, 14.52.
Found: C, 73.81; H, 5.59; Cl, 14.31.

b. From the hydroxy ketone (XIII). In the usual apparatus was placed 25 ml. of benzene in which 20 g. (0.089 mole) of α-hydroxy-α,α-diphenylacetone (XIII) and 7 g. (0.089 mole) of pyridine was dissolved. The flask was cooled in ice to 0°, and 10.5 g. (0.089 mole) of thionyl chloride in 30 ml. of benzene was slowly added through the dropping-funnel. A white solid was formed during this addition. The mixture was heated with stirring for three hours at 50–60°, during which time a green layer separated from the red reaction mixture. The flask was cooled, the layers separated, and the benzene layer extracted twice with 50 ml. of water, sodium bicarbonate, 1% hydrochloric acid, and water. The benzene layer was dried over sodium sulfate overnight, after which the benzene was evaporated at room temperature with a water aspirator. The remaining brown solid was recrystallized from low-boiling petroleum ether to give a light yellow solid, which was then recrystallized from acetone cooled in Dry-Ice to give 17.5 g. (83.3%) of a white solid, m.p. 65–66°. A mixture m.p. with the α-chloro-α,α-diphenylacetone prepared in part *a* showed no depression.

Reaction of α-chloro-α,α-diphenylacetone (I) *with sodium hydroxide in anhydrous ether.* In a three-necked, 500-ml., Morton type flask equipped with a Morton high speed stirrer (14) and a reflux condenser protected with a calcium chloride tube was placed 300 ml. of absolute ether and 2 g. (0.05 mole) of 97% sodium hydroxide pellets. This mixture was stirred until the pellets were finely powdered and then 2 g. (0.008 mole) of α-chloro-α,α-diphenylacetone in 50 ml. of absolute ether was added. The mixture was stirred for four hours at high speed, poured into distilled water, and the layers separated. A 1-ml. aliquot of the water layer was titrated for sodium chloride, and 61% of the original chloride was found to be present as chloride ion. The water layer was then acidified with concentrated hydrochloric acid and a white solid was precipitated. This acid was recrystallized three times from an ethanol-water mixture to give 1 g. (55%) of white crystalline β,β-diphenylpropanoic acid (VIII), m.p. 153–154°. Eijkmann (15) reports m.p. 154–155°.

The *amide* was prepared as white crystals, m.p. 123–124°, in 67% yield. Eijkmann (15) reports m.p. 125–126°. The *anilide* was prepared as white crystals in two forms, m.p. 164–165° and 174–175° in 25% yield. Simons and Archer (16) report m.p. 167° and 175–176°.

The ether-soluble residue from the sodium hydroxide reaction, recrystallized from petroleum ether and then from acetone, gave 0.5 g. (25%) of unchanged α-chloro-α,α-diphenylacetone as a white solid, m.p. 65–66°, mixture m.p. 65–66°.

Reaction of α-chloro-α,α-diphenylacetone (I) *with sodium ethoxide in absolute ethanol.* In a 100-ml. round-bottomed flask fitted with a condenser and a calcium chloride tube was placed 5.4 g. (22 millimoles) of α-chloro-α,α-diphenylacetone in 40 ml. of absolute ethanol. To this solution was added 9.2 ml. of freshly prepared alcoholic sodium ethoxide (2.42 mmoles of NaOEt per ml. of solution). During the addition heat was evolved and the reaction mixture turned brown. After one minute, an aliquot of the solution was titrated with standard hydrochloric acid which showed that 19.8 millimoles (89.2%) of sodium ethoxide was used. The solution was poured onto ice, the water layer neutralized with hydrochloric acid, and the organic material extracted with ether. The ether was distilled from the combined ether layers at room temperature with a water aspirator. The residue, which consisted of 4.75 g. of a dark yellow oil was distilled to give 4.5 g. (85%) of ethyl β,β-diphenylpropionate, b.p. 129–133° (0.3 mm.), m.p. 19–22°; n_D^{25} 1.4850.

Anal. Calc'd for $C_{17}H_{18}O_2$: OC_2H_5, 17.72. Found: OC_2H_5, 17.56.

From the ester fraction was taken 0.178 g. which was treated with alcoholic sodium hydroxide to give 0.16 g. (100%) of a white solid, m.p. 153–154°. A mixture m.p. with β,β-diphenylpropanoic acid previously prepared showed no depression.

An *amide* prepared from this acid was obtained as white crystals, m.p. 122–123°, in 70% yield. The mixture m.p. with the authentic amide was not depressed.

Preparation of α′-chloro-α,α-diphenylacetone (II). Approximately 2.8 g. (0.06 mole) of diazomethane in 100 ml. of dry ether was prepared from 10 g. of nitrosomethylurea. To this stirred solution in the usual apparatus was added over 15 minutes 6.91 g. (0.05 mole) of diphenylacetyl chloride in 10 ml. of absolute ether. A copius evolution of nitrogen occurred. After standing for two hours the solution was cooled in ice, and gaseous hydrogen chloride was passed in for three hours. Most of the nitrogen was evolved within the first one-half hour, after which the solution was orange in color. About 100 ml. of water was added with the violent evolution of gases. The ether layer was separated and washed twice with 5% sodium carbonate, then with water, and finally was dried over calcium chloride. The ether was evaporated at room temperature and reduced pressure to give 7.3 g. (98%) of a white crystalline α′-chloro-α,α-diphenylacetone, m.p. 66–67°. This compound depressed the melting point of α-chloro-α,α-diphenylacetone prepared previously.

Anal. Calc'd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.31; Cl, 14.52.
Found: C, 73.54; H, 5.25; Cl, 14.20.

Reaction of α′-chloro-α,α-diphenylacetone (VII) *with sodium ethoxide in absolute ethanol.* In a 125-ml. Erlenmeyer flask was placed 4 g. (0.0163 mole) of α′-chloro-α,α-diphenylacetone in 50 ml. of absolute ethanol. As soon as the ketone was completely dissolved in ethanol, 21.4 ml. of freshly prepared sodium ethoxide (0.76 mmole of NaOEt per ml.) solution was added, and the reaction heated to reflux. At the end of 1.5 minutes, 92.1% of the sodium ethoxide was used as determined by titration with standard hydrochloric acid. At the end of four minutes, the solution was dark brown in color, and only 0.4% of the sodium ethoxide remained. The solution was then poured onto ice, and the water layer extracted with ether. The combined ether layers were dried over sodium sulfate, and the ether distilled at room temperature with a water aspirator. Distillation of the residual liquid gave a 69% yield of ethyl β,β-diphenylpropionate, b.p. 128–133° (0.3 mm.); n_D^{23} 1.4850. The infrared spectrum of this ester was identical with that ester isolated from the action of sodium ethoxide on I. A 1.1-g. sample of the ester was saponified with alcoholic sodium hydroxide to give 1 g. of β,β-diphenylpropanoic acid, m.p. 153–154°. Mixture melting points of this acid as well as the amide derivative with authentic samples were not depressed.

The water layer was acidified with hydrochloric acid to give 0.5 g. of white needles, m.p. 145–146°. This acid proved to be diphenylacetic acid by a mixture melting point determination with an authentic sample as well as by preparation of the amide and a mixture melting point with an authentic amide. In addition, 0.1 g. of a second acid, m.p. 117–120°, was isolated from the water layer.

SUMMARY

A method of preparation and the proof of structure is reported for the isomeric chloro-α,α-diphenylacetones. A study of the reaction of each of these chloroketones with base indicates that β,β-diphenylpropionic acid or an acid derivative is the main product.

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